Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 145–148

A formal total synthesis of crocacin C

J. S. Yadav,* P. Venkatram Reddy and L. Chandraiah

Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500 007, India

Received 23 August 2006; revised 19 October 2006; accepted 26 October 2006
Available online 17 November 2006

Abstract—An efficient total synthesis of a potent antifungal and moderate cytotoxic agent crocacin C is described. The synthesis involves the generation of four contiguous stereogenic centres via desymmetrization of a meso bicyclic dihydrofuran using asymmetric hydroboration.

Crocacins A–D (**1**–**4**) are a group of compounds found in the extracts of *Chondromyces crocatus* and *Chondromyces pediculatus*.[1] The crocacins moderately inhibit Gram-positive bacteria and are potent inhibitors of animal cell cultures, several yeasts and fungi. Crocacin D possesses the highest activity against *Saccharomyces cerevisiae* as well as higher toxicity in L929 mouse fibroblast cell culture.[2]

The crocacins are polyketide-derived dipeptides with four contiguous stereocentres, consisting of a 6-aminohexenoic or hexadienoic acid and up to five double bonds. The relative configurations of these compounds were deduced using 2D NMR experiments and molecular modelling studies, [2] and their absolute configurations were confirmed by total synthesis.[3–5] The interesting biological profile and structural features of crocacins have attracted several synthetic chemists worldwide towards stereoselective total syntheses as well as construction of intermediates.[6]

In continuation of our ongoing programme of synthesizing polyketide natural products by applying a desymmetrization strategy, we embarked on the total synthesis of crocacins. Herein, we describe the stereoconvergent synthesis of an advanced intermediate, a linear trienoate, for the synthesis of crocacin C utilizing asymmetric hydroboration, cross-metathesis and modified Julia olefination reactions.

A retrosynthetic analysis of **1** is shown in Figure 1, which illustrates that crocacin C could be constructed by coupling aldehyde **5** and 2-benzothiazolyl-sulfone **6** via a modified Julia olefination reaction. Intermediate **5** could in turn be prepared by cross-metathesis of styrene and olefin **7**, which could be synthesized from lactone **8**.[7]

The synthesis of fragment **5** began with bicyclic lactone **8**. Benzyl and *p*-methoxybenzyl ether analogues of lactone **8** have been synthesized earlier by our group and successfully employed for the synthesis of fragments of rifamycin,[8] discodermolide,[9] scytoficin[10] as well as the total syntheses of prelactone B[11] and membrenone C.[12]

Acid catalyzed methanolysis of the bicyclic lactone **8** proceeded smoothly to furnish ester **10** in 80% yield. Lithium aluminum hydride mediated reduction of the ester afforded the primary alcohol in 92% yield, which was subsequently converted into iodide **11** using I_2, PPh_3 and imidazole.[13] Base catalyzed elimination[14] of iodide resulted inolefin **7**, which was converted to aldehyde **12** via dihydroxylation and sodium periodate promoted cleavage. An attempt was made towards the synthesis of compound **14** by modified Julia olefination[15] of aldehyde **12** with benzothiazol-2-benzyl sulfone **13** but this resulted in poor and inconsistent yields (50% from **7**). This prompted us to modify the synthetic strategy, by employing olefin **7** in cross-metathesis reaction[16] with styrene to obtain **14**. Accordingly, olefin **7** was treated with styrene using Grubbs' II generation catalyst (10 mol %) in benzene[17] at 55 °C to furnish the *trans*-styrene derivative **14** in 81% (98:2/*E*:*Z*) yield (see Scheme 1).

Keywords: Crocacin; Desymmetrization; Cross-metathesis; Modified Julia olefination.
* Corresponding author. Fax: +91 40 27160512; e-mail: yadavpub@iict.res.in

0040-4039/$ - see front matter © 2006 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2006.10.141

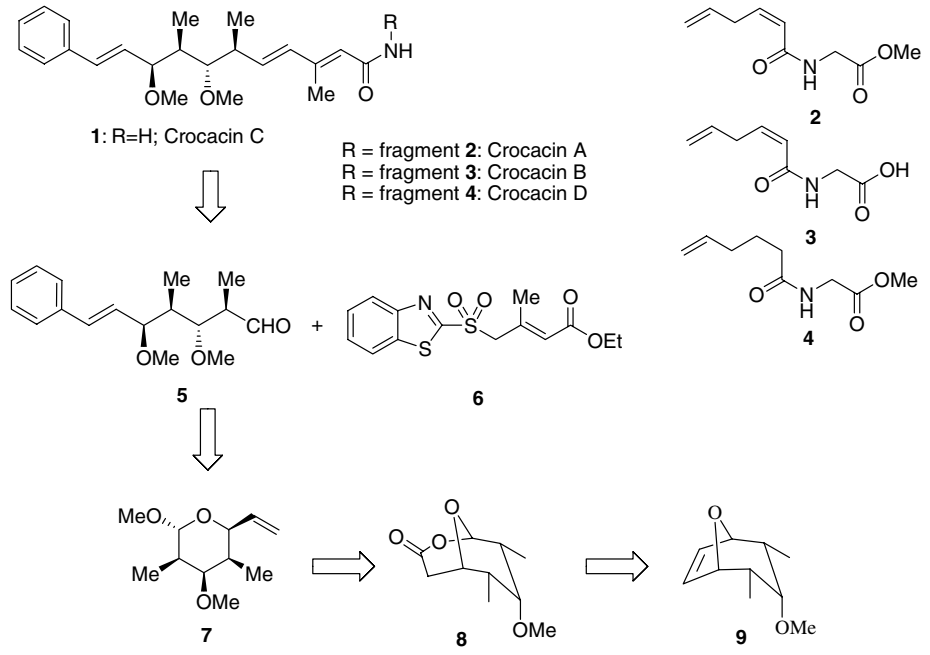
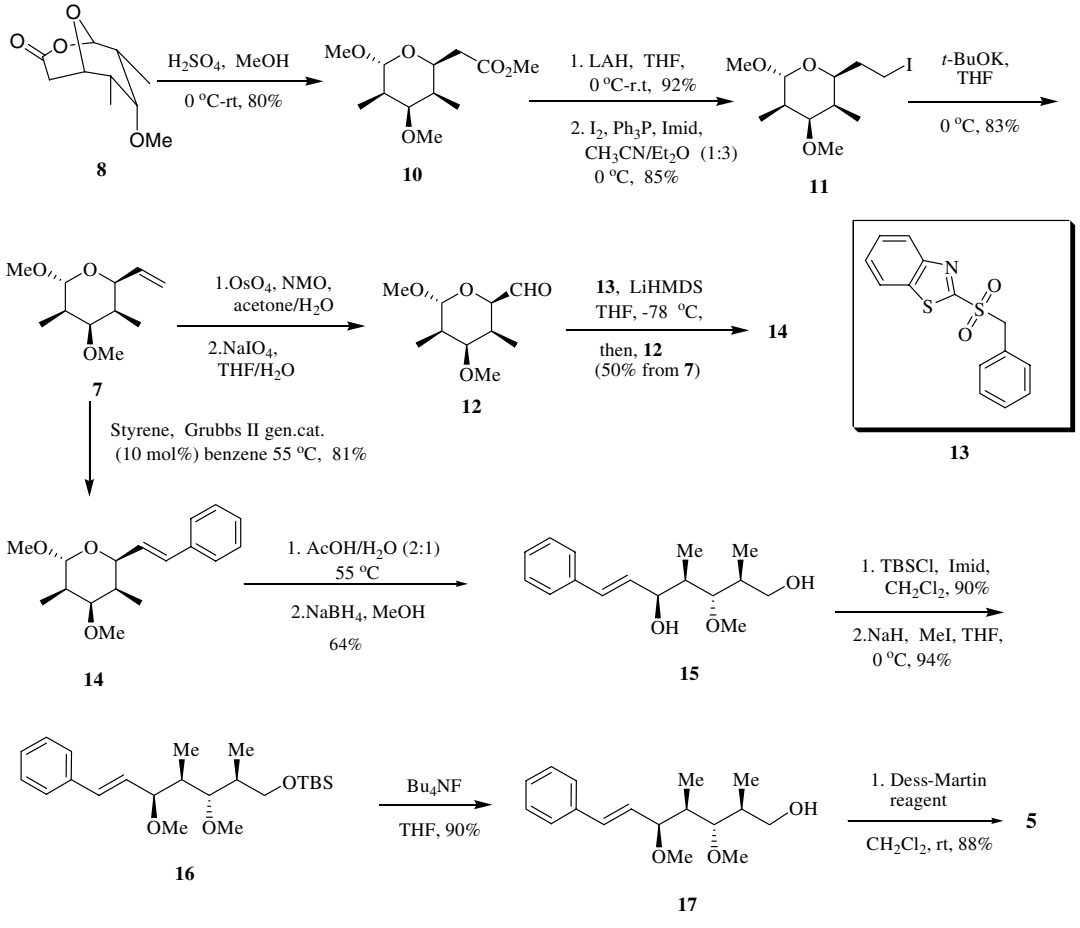
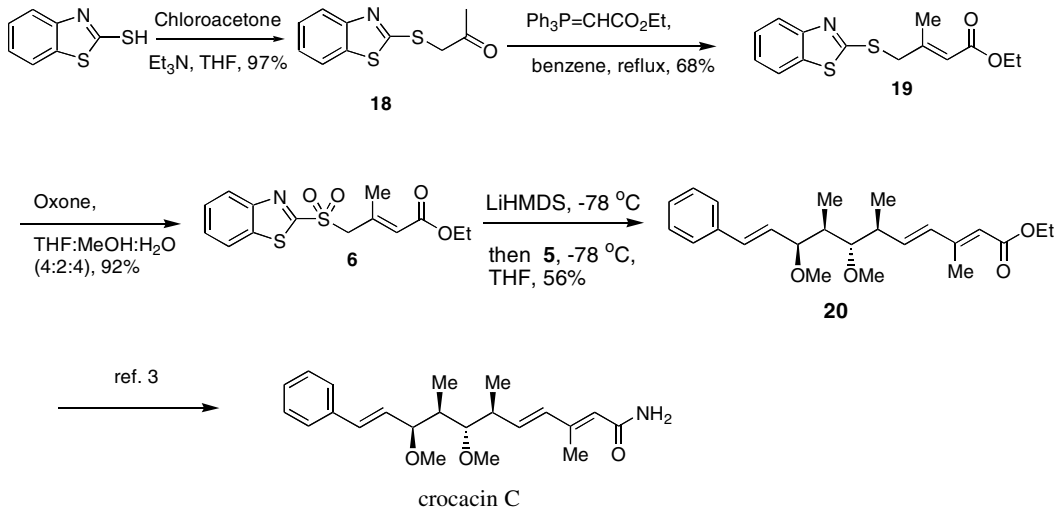


Figure 1.



Scheme 1.

Aqueous acetic acid induced hydrolysis[18] of lactol-ether **14** followed by sodium borohydride mediated reduction of the resultant lactol yielded 1,5-diol **15** in 64% yield. Selective protection of the primary hydroxyl group as



Scheme 2.

its TBS ether was effected by TBSCl and imidazole, and then methylation of the secondary hydroxyl group using NaH and MeI furnished dimethyl ether **16**. Desilylation gave the known alcohol **17**[19] in 76% yield (from **15**), which upon Dess–Martin oxidation[20] furnished aldehyde **5**.

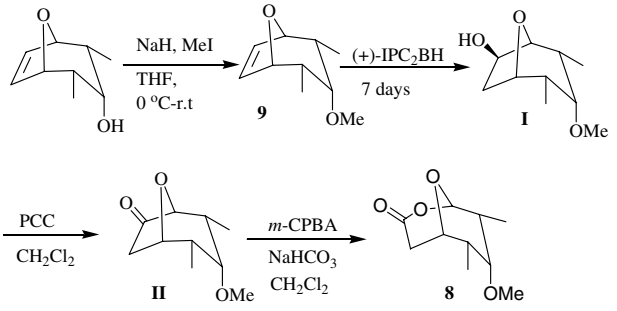
Sulfone **6** was synthesized from mercaptobenzothiazole (MBT) and chloroacetone in the presence of triethylamine shown in Scheme 2. Thus, treatment of mercaptobenzothiazole with chloroacetone furnished **18**. Subsequent Wittig reaction with the stabilized ylide ($Ph_3P=CHCO_2Et$) gave α,β-unsaturated ester **19**. Selective oxidation of the sulfide of **19** with oxone afforded sulfone **6** (61% yield from MBT).

Finally, fragments **5** and **6** were coupled via modified Julia olefination.[15] Accordingly, pre-lithiated sulfone **6** was treated with aldehyde **5** at −78 °C to furnish trienoate **20**, a known intermediate[19] for the synthesis of crocacins A–D,[3] in 56% yield.

In conclusion, the formal total synthesis of crocacin C has been achieved in a stereocontrolled manner by the creation of four contiguous chiral centres via desymmetrization, a *trans*-styrene derivative by Grubbs cross-metathesis and a linear trienoate via modified Julia olefination.

References and notes

1. Kunze, B.; Jansen, R.; Höfle, G.; Reichennach, H. *J. Antibiot.* **1994**, *47*, 881.
2. (a) Jansen, R.; Washausen, P.; Kunze, B.; Reichenbach, H.; Höfle, G. *Eur. J. Org. Chem.* **1999**, 1085; (b) Kunze, B.; Jansen, R.; Sasse, F.; Höfle, G.; Reichenbach, H. *J. Antibiot.* **1998**, *51*, 1075.
3. (a) Feutrill, J. T.; Lilly, M. J.; Rizzacasa, M. A. *Org. Lett.* **2000**, *2*, 3365; (b) Chakraborthy, T. K.; Jayaprakash, S. *Tetrahedron Lett.* **2001**, *42*, 497; (c) Dias, L. C.; de Oleveira, L. G. *Org. Lett.* **2001**, *3*, 3951; (d) Chakraborthy, T. K.; Jayaprakash, S.; Laxman, P. *Tetrahedron* **2001**, *57*, 9467.
4. (a) Feutrill, J. T.; Lilly, M. J.; Rizzacasa, M. A. *Org. Lett.* **2002**, *4*, 525; (b) Chakraborthy, T. K.; Laxman, P. *Tetrahedron Lett.* **2002**, *43*, 2645; (c) Crowely, P. J.; Aspinall, I. H.; Gillen, K.; Godfrey, C. R. A.; Devillers, I. M.; Munns, G. R.; Sageot, O. A.; Swanborough, J.; Worthington, P.; Williams, A. *J. Chim.* **2003**, *57*, 685; (d) Dias, L. C.; de Oleveira, L. G.; Vilcachagua, J. D.; Florian, N. *J. Org. Chem.* **2005**, *70*, 2225.
5. (a) Chakraborthy, T. K.; Laxman, P. *Tetrahedron Lett.* **2003**, *44*, 4989; (b) Feutrill, J. T.; Rizzacasa, M. A. *Aust. J. Chem.* **2003**, *56*, 783.
6. (a) Gurjar, M. K.; Khaladkar, T. P.; Borhade, R. G.; Murugan, A. *Tetrahedron Lett.* **2003**, *44*, 5183; (b) Raghavan, S.; Reddy, S. R. *Tetrahedron Lett.* **2004**, *45*, 5593.
7. The synthesis of lactone **8** is similar to the preparation of its benzyl and *p*-methoxybenzyl analogues; see Ref. 9,



8. Yadav, J. S.; Rao, C. S.; Chandrasekhar, S.; Ramarao, A. V. *Tetrahedron Lett.* **1995**, *36*, 7717.
9. Yadav, J. S.; Abraham, S.; Reddy, M. M.; Sabitha, G.; Sankar, A. R.; Kunwar, A. C. *Tetrahedron Lett.* **2001**, *42*, 4713.
10. Yadav, J. S.; Ahmed, M. *Tetrahedron Lett.* **2002**, *43*, 7147.
11. Yadav, J. S.; Reddy, K. B.; Sabitha, G. *Tetrahedron Lett.* **2004**, *45*, 6475.
12. Yadav, J. S.; Srinivas, R.; Sathaiah, K. *Tetrahedron Lett.* **2006**, *47*, 1603.
13. Garegg, P. J.; Samuelson, B. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2866.
14. Sylvestre, I.; Olliver, J.; Salaun, J. *Tetrahedron Lett.* **2001**, *42*, 4991.

15. (a) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563; (b) Harris, J. M.; O'Doherty, G. A. *Tetrahedron* **2001**, *57*, 5161; (c) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26.
16. For reviews on olefin metathesis, see: (a) Grubbs, R. H.; Trnka, T. M. *Acc. Chem. Res.* **2001**, *34*, 18; (b) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900; (c) Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.
17. Quinn, K. J.; Isaacs, A. K.; Christopher, B. A. D.; Szklarz, S. C.; Arvary, R. A. *Org. Lett.* **2005**, *7*, 1243.
18. Snider, B. B.; Song, F. *Org. Lett.* **2001**, *3*, 1817.
19. The spectral and physical data of alcohol **17** and ester **20** matched in all respect with reported data (Ref. 3). *Selected physical data for compound* **17**: clear oil; R_f 0.3 (EtOAc/hexane 25:75); $[\alpha]_D^{20}$ −3.8 (*c* 1.80, CH_2Cl_2). Compound **20**: light yellowish oil, $[\alpha]_D^{20}$ −6.7 (*c* 0.2 $CHCl_3$). Compound **7**: colorless oil. R_f 0.5 (EtOAc/hexane 10:90); $[\alpha]_D^{20}$ −94.7 (*c* 0.87, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.87–5.76 (m, 1H), 5.28 (dt, 1H, $J = 17.3$, 1.5 Hz), 5.25 (dt, 1H, $J = 10.5$, 1.5 Hz), 4.52 (s, 1H), 3.57 (t, 1H, $J = 5.2$ Hz), 4.27–4.25 (m, 1H), 3.31 (s, 3H), 3.29 (s, 3H), 2.11–1.98 (m, 2H), 1.00 (d, 3H, $J = 7.5$ Hz), 0.87 (d, 3H, $J = 6.7$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 136.6, 115.2, 103.5, 77.6, 71.4, 56.0, 54.6, 36.4, 35.9, 12.8, 8.9; HRESIMS: Calcd for $C_{11}H_{20}O_3Na$ [M+Na$^+$]: 223.1310. Found: 223.1300. Compound **14**: light yellowish oil; $[\alpha]_D^{20}$ −64.7 (*c* 1.90, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.15 (m, 5H), 6.60 (d, 1H, $J = 15.9$ Hz), 6.20 (dd, 1H, $J = 15.9$, 6.6 Hz), 4.58 (s, 1H), 4.45 (m, 1H), 3.60 (t, 1H, $J = 5.1$ Hz), 3.34 (s, 3H), 3.33 (s, 3H), 2.17–2.05 (m, 2H), 1.04 (d, 3H, $J = 7.9$ Hz), 0.92 (d, 3H, $J = 7.9$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 132.1, 130.4, 128.5, 128.3, 127.4, 126.4, 103.6, 77.9, 77.0, 71.5, 56.2, 54.2, 36.6, 12.9, 9.3; mass (ESI): *m*/*z* 299 [M+Na$^+$]. HRESIMS: Calcd for $C_{17}H_{24}O_3Na$ [M+Na$^+$]: 299.1273. Found: 299.1261. Compound **6**: white solid; mp: 68–70 °C; IR ν_{max} (film): 2994, 2951, 1769, 1699, 1438, 1333, 1285, 1154, 1035, 861 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20 (d, 1H, $J = 9.2$ Hz), 8.00 (d, 1H, $J =$ 6.9 Hz), 7.55–7.68 (m, 2H), 5.78 (s, 1H), 4.26 (s, 2H), 4.08 (q, 2H, $J =$ 13.8, 6.9 Hz), 2.33 (s, 3H), 1.24 (t, 3H, $J =$ 6.9 Hz); mass (ESIMS): *m*/*z* 348 [M+Na$^+$], 326 [M+H$^+$].
20. Dess, D. B.; Martin, J. C. J. *J. Am. Chem. Soc.* **1991**, *113*, 7277.